AMERICAN Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

APPARATUS USED IN MEASURING RADIATION

Since 1825 *August 1956*

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription $4.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents — Back Numbers, 50 Cents

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 128 AUGUST 1956 No. 8

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EDITORIAL

THE LONG RANGE HAZARDS OF RADIATION

ONE of the most important scientific documents of recent times is the report of the Committee on Genetic Effects of Atomic Radiation. This was one of six reports prepared by the National Academy of Sciences in its study of the biological effects of atomic radiation.

There has been some criticism of this report because of its rather pessimistic nature and those reading it carefully may be inclined to pessimism but this is not the fault of the committee nor due to any magnification by them of the potential hazard. Indeed, their report is a very profound and carefully worded document which cannot help but impress one with the precise, scientific approach which was used and the desire to publish as clear a picture as possible of this problem regardless of its impact on public opinion. The report of this committee or its conclusions deserves wide reading—not only by scientists but by all laymen who wish to be well-informed. The reader is referred to the June 29th issue of *Science* where the major portion of the text of the summary report is published.

It is not possible to abstract this report fully nor even to give all of its major conclusions, but we do wish to comment briefly on some of the points which cannot be given too much publicity. First, all radiation of the ionizing type, including gamma rays and x-rays, are harmful and, from the standpoint of the mutation which they cause in our genes, their effects are cumulative. For this reason, small amounts of radiation spread over a period of time are just as damaging as a single exposure to a higher intensity of radiation. There are undoubtedly many mutations produced in the population by background radiation which during a person's first thirty years of life totals about 5 roentgens. Such background radiation, including that caused by cosmic rays, cannot be eliminated by any practical means.

A considerable amount of radiation is absorbed by many diagnostic and therapeutic procedures such as with the use of x-rays and radioisotopes and, here in particular, the medical profession quite unknowingly has been careless in the past. The fact is that few radiologists have even the slightest idea of what the output of their

x-ray machine is and often use a much higher intensity than is needed for the purpose at hand. They have, furthermore, been quite careless in not protecting the reproductive organs wherever possible since it is here that the hereditary germinal cells reside and it is in these cells that mutations having genetic effects take place. It is suggested that every person should have a permanent record kept of all radiation to which he or she has been exposed and that, except in great emergencies, it not be permitted to exceed a certain figure. This does not mean that there is any safe level of radiation, for it is all harmful regardless of how small. The use of fluoroscopy should be restricted as much as possible since this device generally produces more radiation than does roentgenography.

There is every reason to believe that, in this age of atomic energy, we can expect the amount of radiation to which a person is exposed to increase. Some little of this may be due to atomic "fallout". This presently is not a very significant source except to some few unfortunate people who may be accidentally exposed near the site of an atomic explosion. The use of atomic energy as a source of industrial power and the accumulation and disposal of atomic waste seem destined to be serious problems which will require a solution. Unfortunately, it may be highly desirable to expand our atomic energy facilities as a means of furthering human progress, but it is not likely that this can be done without paying some price genetically in future generations. Very careful decisions will need to be made to make sure that the progress made justifies the cost in terms of genetic damage and, at this moment, this cost is not easy to evaluate.

Most of the present knowledge on the damaging effects of radiation-induced mutations has been obtained using the fruit fly and mice, but there is no reason to believe that the effect on humans is not strictly parallel. Since the damage takes place on the genes themselves, it is believed that the effects would be similar on all living forms inasmuch as, at the cell level, mechanisms are surprisingly uniform.

When one contemplates that genetic damage can carry through for generation after generation, it is a rather somber thought to say the least. The impact on the human race may be even more significant by reason of the fact that many weakened individuals no longer succumb to the law of the survival of the fittest. Even today we manage to perpetuate in the human race countless thousands who would have died were it not for modern medicine. To still further increase the num-

bers of abnormal and handicapped individuals as the result of still greater genetic damage through radiation might well influence the whole course of human destiny.

Again, we say the committee in its findings was not unduly pessimistic, but no-one can read this report without coming to the conclusion that we should go slowly in our rapid expansion of atomic energy and that, above all, we should begin at once carefully planned studies to estimate more fully the impact of genetic damage caused by radiation. At the moment, we only have fairly conservative opinions from our experts who unfortunately do not have any wealth of scientific data on which to depend. The medical profession should also contribute in every way possible in reducing radiation to germinal tissue, particularly in young patients.

Other committees of the National Academy of Sciences have reported or are to report on other biological aspects of radiation such as the direct pathologic effects, the effects on agriculture, etc. and each of these will be a great contribution to our present understanding of radiation hazards.

In conclusion, we cannot help but reflect that, with each new discovery which man makes, he finds that it is not an unmitigated blessing. As with all human achievements, it proves to be both good and bad and sometimes it is almost impossible to tell whether the good outweighs the bad. No-one but an incorrigible optimist can feel completely at ease concerning the long range effects of this new force which man has unleashed. It could give man a much longer tenure on this planet or it could even now be planting the seeds of his destruction.

L. F. Tice

THE COLORIMETRIC DETERMINATION OF PROTEOLYTIC ACTIVITY IN ANIMAL GASTRIC JUICE

Morton E. Goldberg and G. Victor Rossi *

INVESTIGATION, currently being conducted at the LaWall Memorial Laboratory of Pharmacology and Biochemistry, into the effects of anti-ulcer agents on gastric secretion have necessitated the development of an accurate method for the determination of proteolytic activity in animal gastric juice. The method employed in our study is an adaptation of Wesselman's modification (1, 2) of Anson's procedure (3). The technique consists essentially of the digestion of hemoglobin by pepsin at a pH of 1.6 to 2.0. Within this pH range the hemoglobin is acted upon by proteolytic substances with the subsequent liberation of amino acids, primarily tyrosine and tryptophane. The addition of a phospho-molybdic acid reagent in alkali to the hemoglobin substrate results in the development of a blue color, the intensity of which is proportional to the amount of pepsin present. In the original procedure (3), tyrosine was used to develop a reference color. Hunt (4) employed dried plasma as a substrate and a standard phenol solution to develop a reference color.

Other methods which have been employed for the estimation of proteolytic activity include the photometric method of Riggs and Stadie (5), which is based upon the measurement of the decrease in turbidity of a suspension of coagulated egg white. The method of Mett (6), and its subsequent modifications, is also based upon peptic digestion of albumin. In this procedure, small glass tubes are filled with coagulated egg albumin and added to a solution containing pepsin. After a suitable period of incubation, the length of the column of albumin digested is measured by means of a microscope and a millimeter scale. Volhard and Lohlein (7) have measured proteolytic activity by adding the material to be tested to casein solution, salting out the unreacted casein, and estimating the digestion products by titration of the filtrate.

In the procedure to be described, N. F. X. Reference Pepsin is employed as the standard and the proteolytic activity of gastric

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juice is expressed as the equivalent of Reference Pepsin. Using this relatively rapid technique, we have obtained consistently accurate and reproducible results. A further advantage over former methods is that results are expressed on a weight basis rather than a unit basis. It may be noted that little uniformity exists among the various units of pepsin activity employed by different investigators.

As Wesselman has shown (1), the standard curve obtained with a solution of Reference Pepsin varies from day to day depending upon changes in substrate and temperature. However, the results obtained on any given day are reproducible. For this reason the standard curve is repeated with each group of determinations.

Method

A standard curve of pepsin activity is determined by dissolving 100 mg. of N. F. X. Reference Pepsin and 300 mg. of NaCl in sufficient 0.3% HCl to make 150 ml. Aliquots of this artificial gastric fluid are added to a 100 ml. volumetric flask containing 20 ml. of a 2.5% Bactohemoglobin solution and 5 ml. of 0.5 N HCl. Digestion is allowed to proceed for 15 minutes at 25° C., after which time, 10 ml. of cold 25% trichloracetic acid is added to the flask, the mixture shaken thoroughly and brought to volume with distilled water. The solution is then filtered through Whatman No. 1 filter paper and the first few drops of filtrate are discarded. To 10 ml. of the filtrate, 10 ml. of 0.5 N NaOH and 1.0 ml. of Folin phenol reagent (8) are added and gently agitated in a 50 ml. volumetric flask. The solution is then adjusted to volume with distilled water and read in a colorimeter with a suitable filter. Experiments have shown that optimum color develops within 15 minutes and lasts for 40 minutes. Therefore, the solutions are always read 30 minutes after the development of color.

In preliminary experiments, rats have been employed as the source of gastric fluid. The gastric samples are obtained by the methods of Shay et al. (9), Friedman (10), and others. The technique consists essentially of ligating the pyloric portion of the stomach, under light ether anesthesia, of previously fasted rats. The wound is closed and the animal quickly recovers. After a predetermined time interval, the animal is again anesthetized and the stomach carefully removed. The volume of the gastric fluid is recorded and the contents transfered to a centrifuge tube and centrifuged at 20,000 RPM

for 10 minutes. A 0.33 ml. aliquot of the supernatant is added to the substrate and the assay is concluded as outlined above. A "blank" is prepared by subjecting another 0.33 ml. aliquot to the same procedure, omitting prior digesting with the substrate. Any color which develops in the "blank" is subtracted from the colorimeter reading obtained with the gastric fluid-substrate mixture. The results are expressed as "proteolytic activity equivalent to mgs. of N. F. X. Reference Pepsin." The normal range of activity may be determined by preliminary experimentation. Refinements in the standard curve can thus be made affording greater accuracy in that region of the curve corresponding to the degree of activity most frequently measured.

Results obtained thus far indicate the limits of accuracy of the method presented above to be ± 3%. Repetition of assays performed with the Klett-Summerson Colorimeter, Bausch and Lomb Spectrophotometer and the Beckman Spectrophotometer, Model DU, indicate that any suitable colorimeter may be employed in these determinations.

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THE ESTIVIN-HISTAMINE COMPLEX

Alfred Halpern * and A. J. MonteBovi **

THE distressing ophthalmic symptomatology associated with allergic pathology is perhaps one of the more difficult problems to control with either locally and systemically administered therapy. Whether the failure to relieve the itching, smarting and tearing of the eyes of the allergic patient is due to a lack of active material at the local affector site or to an inherent inability of the therapeutic agent to completely neutralize the stimulating factors is the problem which remains to be answered since there are many complexities associated with the elaboration of a mechanism of histamine antagonism.

The relationship between chemical structure and antihistaminic activity has been investigated by many workers (1, 2, 3). Generally it has been demonstrated that antihistaminic drugs may be divided into two broad categories of pharmacologic behavior—(a) those which are competitive antagonists to the histamine molecule and (b) those which are non-competitive spasmolytics (4, 5). The concentration of antagonists in relationship to histamine at the affector site is the principal determinant of the effectiveness of medication included in group A—while the potency of a compound of group B measures the degree of relief obtained.

In many instances the presence of undesirable side effects associated with the amount of antagonist required to counteract local hayfever symptoms results in a lowered dosage being administered and consequently only partial relief is achieved. When local instillation is utilized difficulties of absorption, as well as of inherent drug irritation, frequently limit the effects obtained. It is not surprising, therefore, to note the contrasts in the degree of relief obtained among the different agents used against histamine-mediated symptomatology.

In studying the role of histamine in the ophthalmic symptomatology associated with allergic conjunctivitis, hayfever and contact

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irritants, the role of the non-antihistaminic, natural products in controlling these distressing complaints are particularly impressive. A special galenical preparation, Estivin, an extract of Rosa galica, L., is described as having a superior local effect over the antihistaminic agents. Although this product has been available for years, Shaftel (6) notes that "there has not been a single newer product introduced which afforded us either a more effective response or a safer effect." The use of this particular preparation is also recommended by Urbach (7) for the relief of ophthalmic hayfever symptoms.

Estivin instilled into the eye exerts a purely local effect. It does not have nervous system mediated action nor is it absorbed to produce a systemic blood level. Its rapidity of action, which has been described as beginning within five minutes (6) would indicate the direct modification of the histamine molecule or an interference with its activity.

When Estivin is mixed with a solution of histamine phosphate, an amorphous precipitate develops almost immediately. On centrifuging and washing this precipitate, a fine, amorphous, yellow powder is obtained which has an indefinite melting-point. It is insoluble in water, saline solution and plasma but is made soluble by treatment with strong alkali and acid solutions. The precipitated material is soluble in ethanol, partially soluble in acetone and insoluble in ether and chloroform.

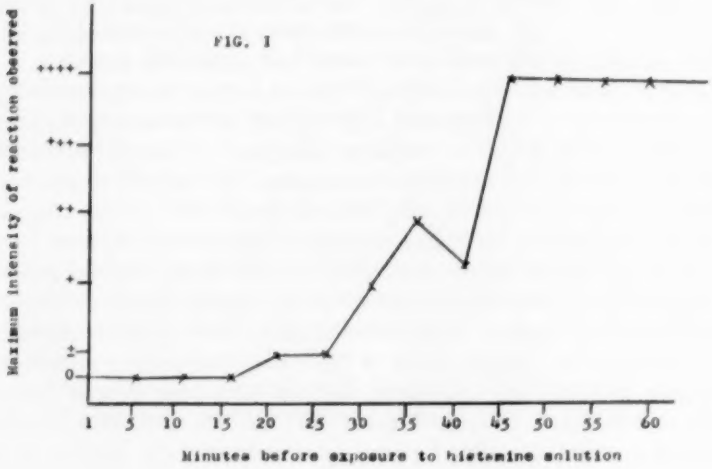
On mild alkaline hydrolysis and acidification, histamine is obtained. This would indicate that the precipitate is formed by the inter-reaction of histamine with Estivin and apparently results in the formation of an insoluble-complex. From a study of the stoichiometry of the reaction, it is established that 0.25 ml. of Estivin are required to complex with 1 mg. of histamine phosphate. The pharmacologic properties of the Estivin-histamine complex was studied in the rabbit's eye and in the guinea pig. Two drops of 0.1% (w/w) suspension of the complex in Ringer's solution, was instilled into the eyes of a 2 kg. albino rabbit, and observed periodically for 36 hours. There was no evidence of a histamine reaction or of any irritation of either the corneal or conjunctival tissues. The control solution of 1×10^{-4} gm./ml. concentration of histamine instilled in an identical manner produced an ophthalmic reaction persisting over 6 hours. The experiment was repeated using different concentrations of complexed material and the response again indicated the absence of a

reaction. It appears that Estivin neutralizes the action of histamine by altering its solubility by forming a complex.

In order to study the kinetics of the complexing phenomenon in vivo, two series of experiments were conducted. By instilling the Estivin into the eyes of a guinea pig immediately before exposure to a histamine solution, the degree of protection against the reaction could be ascertained. By varying the time interval between the different instillations, the duration of any protective effects would be determined.

The rate of the complexing reaction determined in vitro indicated that it was almost instantaneous and was not effected by temperature or by pH over the range of pH 4 to pH 7.8.

One drop of Estivin was instilled into one eye of a guinea pig which was then exposed to an aerosol fog of histamine phosphate (1×10^{-4} gm./ml. equivalent to the histamine base). The interval between the instillation of Estivin and exposure to histamine was varied from one minute to one hour. The eyes were observed over an interval of 36 hours and the experiments repeated after a three-day rest period, utilizing the same animals. The results indicated that Estivin is capable of ameliorating effect of histamine in vivo. This protective effect was evident for approximately twenty minutes (Fig. I).



By inverting the order of exposure to these agents the effects of the complexing reaction on the reversal of established symptoms could be studied. A histamine reaction was allowed to develop in guinea pigs by an aerosol-fog technique. The course of the reaction was studied and the intensity per unit time chartered. After two days rest, the animal was again exposed to the histamine-fog solution and the Estivin added at the ¼, ½ and ¾ reaction life times. The modification of the subsequent course of the reaction was compared with the control curve in order to evaluate the effects of the Estivin.

The Estivin markedly shortened both the intensity and the duration of the reaction curve during the ascendent phase and to a lesser degree altered the course of the descendent phase of the histamine reaction on the eyes.

Discussion

The Estivin apparently neutralizes the physiologic properties of histamine and consequently may be considered to be a form of an antihistaminic. However, this should be differentiated from the conventional antihistaminics since it apparently exerts its action through a different rationale.

The complexing reaction between the Estivin and the histamine results in an insoluble molecule. It is well known that insoluble materials do not exert the pharmacologic activity of its soluble homologue. The removal from the site of activity of the histamine apparently accounts for the palliative action resulting after the administration of Estivin. Thus, the rationale for the activity of Estivin may be derived from the physico-chemical properties of the complexing reaction rather than to a pharmacologic mechanism. It is the absence of a physiologic basis of activity, that is a principle difference between Estivin and the conventional antihistaminic compounds with regard to the neutralization of histamine. In addition to the histamine complexing properties, Estivin exerts a mild astringent-decongestant action common to certain aqueous plant extracts. This astringent-decongestant property augments the reversal of the histaminic reaction.

The above rationale is in agreement with the reported (6) excellent symptomatic relief obtained after the use of Estivin. The finding that Estivin exerts a rapid palliative action is consistent with the pattern of the complexing phenomena.

The favorable alteration of the reaction curve by Estivin (Fig. II) indicates that optimal results are obtained if Estivin is administered early in the development of the symptomatology. In view of the dynamic nature of the precorneal film, it is doubtful that a high order of sustained complexing ability is obtained. The sustained effects of Estivin are apparently due to the adjuvant decongestive and astringent properties.

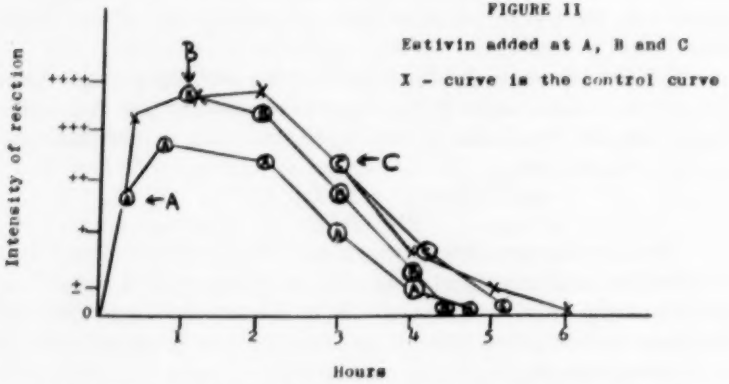


FIGURE II

Estivin added at A, B and C

X - curve is the control curve

The purely local site of action of Estivin is important to the overall therapeutic management of the patient. Since the mechanism of action is due to a physico-chemical, rather than a physiologic, medium, there is no interference with desensitizing procedures or with the overall activity of other drugs used. Estivin may be used in conjunction with all forms of medication and densensitization regimens.

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THE CHEMICAL TREATMENT OF HODGKIN'S DISEASE

John R. Sampey *

MORE than half of the current investigations on the chemical treatment of Hodgkin's disease (HD) deal with the use of nitrogen mustards and triethylene melamine. Cortisone, ACTH, radioactive isotopes and antibiotics constitute other leading chemicals in the management of HD. The present paper presents a score of chemical agents in 131 clinical studies of this neoplastic disease.

Nitrogen Mustards. In 1949 Erf and Bauer (36) treated 43 patients with HN_2 and reported good remissions. Nabarro (81) had remissions lasting 3 to 12 months with this chemical. Tucker and Kay (119) recorded good palliative results in two-thirds of 24 patients on this therapy, but Videbaek (120) considered the treatments caused more discomfort and involved more risk than x-irradiation. Huguenin, *et al.* (56), described excellent palliation with HD and lymphosarcoma patients but less success with skin cancers. Ben-Asher (17) found HD patients were helped more by HN_2 than were those with leukemia, lymphosarcoma or lung cancer. Kurnick, *et al.* (66), secured brief remissions in 20 patients with HD, and Meyer and Overmiller (77) noted marked improvement after HN_2 therapy.

In 1950 Dameshek, *et al.* (29), induced remissions of 2 months to 2 years in HD patients with nitrogen mustards, and they considered the chemical more effective than x-rays. Alpert, *et al.* (2), recorded good clinical results with HN_2. In 1951 Goldman (46) described complete but temporary remissions in 3 of 4 patients, and in 1952 Ghanem (45) obtained temporary palliative effects in 25 patients with HD, leukemia, etc. In 1954 Beattie and Howells (15) stated that 21 of 27 patients with HD had good clinical response to nitrogen mustard therapy.

Nitrogen mustards have been employed in combination with x-irradiation. In 1949 Roswit and Kaplan (100) described the role of HN_2 as a systemic adjunct to radiation therapy, and in 1950 Bethell, *et al.* (19), alternated mustards with x-rays in 173 cases.

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In 1951 Gellhorn and Collins (43) noted 78% improvement in patients with both HN_2 and x-ray therapy, while Kieler (64) reported good results in 22 patients with HD given mustards alone and with irradiation. In 1952 Rose, *et al.* (97), combined mustards with single dose irradiation on 52 patients with lymphomata and other neoplasms, and they secured their best results with HD. In 1954 very effective results were reported by Arons and Freeman (5) on the combination of x-rays and mustards with 10 HD cases.

ACTH and cortisone have been used with nitrogen mustard therapy for HD. In 1951 Alpert, *et al.* (3), reported good response with ACTH or cortisone with mustards. In 1952 Justin-Besaneon, *et al.* (60), noted remissions in 110 HD patients with cortisone and mustards. Two years later Hochman and Ickowicz (54) had 11 patients with HD and lymphoblastic diseases who were resistant to nitrogen mustards, respond to the combination of cortisone and mustards, and in 1955 Rollins and Shaw (95) secured good results with ACTH and mustards in combination therapy. McCarthy (68) in 1955 summarized his results on the treatment of neoplasms with the combination therapy of ACTH or cortisone and nitrogen mustards in the following way: 16% of the cases had unusual temporary remissions, 15% showed good palliation and longer life, 29% experienced fair response, and 40% received no help.

Weisberger, *et al.* (124), used L-cysteine prior to HN_2 in order to permit larger doses of the latter. Richmond and Beardsley (93) described a case of nitrogen mustard therapy complicated by acute renal failure due to uric acid crystallization, and Mills (78) reported two toxic cases, one fatal and one near fatal from the use of nitrogen mustards for HD. Roswit and Pisetsky (101) recorded one case of toxic psychosis following HN_2 therapy.

Other investigators reporting good palliation with nitrogen mustards in HD include: Alden and Zbinden (1), Ariel and Kanter (4), Bateman, *et al.* (10), Bollinelli, *et al.* (22), Burnett, *et al.* (27), Dameshek (32), Howells (55), Huguenin, *et al.* (56), Shullenberger, *et al.* (108), Tsevrenis, *et al.* (118), Wintrobe, *et al.* (126).

Beta-Naphthyl-di-2-chloroethylamine. In 1950 Introzzi and Ninni (58), and Mathews (75) reported good results with this naphthyl derivative in HD patients. In 1951 Gardikas and Wilkinson (42) noted 4 of 7 HD patients responded well to this agent, and in 1954 Videbaek and Kaae (121) recorded better results on 25

patients than with nitrogen mustards. In 1955 Ramioul (89) endorsed this drug for HD patients.

TEM. Triethylene melamine, TEM, has been employed almost as extensively as nitrogen mustards in the control of HD. In 1951 Bayrd (11, 12) reported good remissions, and the following year he noted subjective improvement in 6 of 7 patients (13, 14). In 1952 Beizer (16) recorded 2 of 4 HD cases showed clinical help, and Colsky, *et al.* (30), described remissions of 10 days to 2 months in 7 of 10 patients on TEM. In 1952 Conley (31) reported 5 of 6 patients showed remissions, and Erf (37) included 11 HD patients in his study of TEM. Evans and Swirsky (38) found 4 HD patients had less distress on TEM than with mustards or x-irradiation, and Justin-Besancon, *et al.* (60), included TEM in their treatment of 110 HD cases. Kravitz, *et al.* (65), showed 32 of 36 HD patients had partial to excellent remissions with TEM. Prigot, *et al.* (88), had 7 complete and 19 partial remissions in 26 patients with lymphomas, and their best results were with HD cases. Sawitzsky and Meyer (106) noted temporary improvement in 30 patients with HD, and Schwartz (107) described 9 of 16 patients who were helped by TEM therapy.

In 1953 Burtner, *et al.* (28), concluded that TEM was better than HN_2 in the treatment of 38 HD patients, and Paterson, *et al.* (86), stated that two-thirds of their 22 cases had satisfactory remissions. Good results were obtained on 6 HD cases in a report by Lenti and Gavosto (67) in 1953 and the following year Blackburn and King (20) reported that 8 of 14 HD cases showed good remissions. Ortolan (83) employed TEM with $NaHCO_3$ with 44 cases of HD, leukemia and lymphosarcoma. In 1955 Wright, *et al.* (130), noted complete remissions in HD patients given TEM.

Further clinical studies on TEM therapy in HD have been made by Bond, *et al.* (23), Burnett, *et al.* (27), Hansen and Bichel (51, 52), Karnofsky, *et al.* (61, 62, 63), Medal (76), Pavlovsky and Vilasega (87), Rhoads, *et al.* (92), Rottino, *et al.* (103), Rundles and Barton (105), Silverberg and Dameshek (109), Walsh, *et al.* (123), Wintrobe, *et al.* (126), Wright, *et al.* (128, 129, 131).

ACTH and Cortisone. Straus, *et al.* (115), described 7 patients with advanced HD who showed subjective improvement, 3 who had their temperature reduced, but none who experienced a true remission on cortisone therapy. Stickney, *et al.* (112), reduced the size of lymph nodes in HD with cortisone. Temporary remissions with

ACTH or cortisone have been reported by Eliel (33, 34), Griffith and Gutch (49), Marchal (70, 72, 73), Rosenthal, *et al.* (99), Spies, *et al.* (111), and Stickney, *et al.* (113).

Marchal (71) considered cortisone dangerous in HD, because of hemorrhages. Rollins and Shaw (95) used a combination of ACTH and nitrogen mustards with good results, and Hochman and Ickowicz (54) obtained remissions in patients who were resistant to mustard therapy by administering a combination of cortisone and nitrogen mustard. Alpert, *et al.* (3), and McCarthy (68) reported good results in HD with nitrogen mustard and ACTH or cortisone. Farber, *et al.* (40), noted improvement in 66.7% of 243 patients with HD, acute leukemia and lymphosarcoma after the use of folic acid antagonists combined with ACTH or cortisone.

Radioisotopes. In 1949 Herve (53) described a patient with HD who returned to work 6 months after P^{32} therapy. Huguenin, *et al.* (57), observed 5 remissions with P^{32}. Werff (125) recounted better clinical results with this isotope after treatment with Au^{198}, and he also found Bi^{206} useful in HD. Müller and Rossier (80) used Zn^{63} and Au^{198} in HD of the lungs, and Riordan (94) treated a number of lymphatic neoplasms with Au^{198}. Mallet, *et al.* (69), described 2 cases of lymphogranulomatosis which responded to As^{76} therapy, one being in complete remission after 15 months. Marchal (74) claimed limited usefulness of As^{76} in the management of HD, and Block, *et al.* (21), rated the isotope on a par with P^{32}, urethane and x-rays in HD therapy. Romieu, *et al.* (96), employed P^{32} in HD.

Antibiotics. Bertrand-Fontaine, *et al.* (18), treated 15 cases of HD with actinomycin and obtained notable results in 1 and palliation in 2 others. Ravina (90, 91) reported fair results in the use of this antibiotic. Barnard (6, 7, 8, 9) employed terramycin, streptomycin and other antibiotics to secure some palliation with HD patients. Fujii, *et al.* (41), described clinical improvement in a child with HD after sarkomycin therapy. Goldman (46) and Rottino, *et al.* (102), reported negative results with aureomycin in HD.

Colchicine. Grollman, *et al.* (50), obtained striking antipyretic and analgesic effects in HD with colchicine, but remissions were brief. Isch-Wall (59) and Volterra, *et al.* (122), recounted temporary results with this alkaloid. Broun, *et al.* (25), described remissions of 2 weeks to 6 months in 4 of 5 HD cases receiving a combination of

colchicine, desoxycorticosterone and ascorbic acid. Moeschlin, *et al.* (79), reported negative results with the new colchicine alkaloid, Demecolein (Ciba).

TEPA and TETPA. Triethylene phosphoramide, TEPA, induced temporary clinical improvement in HD patients in the reports of Farber, *et al.* (39), Sykes, *et al.* (116), and Wright, *et al.* (129, 130) Smith, *et al.* (110), noted clinical improvement in 9 of 21 children on triethylene thiophosphoramide, TETPA, therapy.

6-MP and TMM. Burchenal, *et al.* (26), found 6-mercaptopurine, 6-MP, was without effect on HD. Paterson and Boland (85) reported trimethylolmelamine, TMM, caused clinical improvement in HD cases.

Azaserine. Ellison, *et al.* (35), lowered the fever in 7 of 19 patients, and induced objective improvement in 5 others with azaserine.

Testosterone. Brocq and Sluczewski (24) treated HD patients with this male hormone.

Folic Acid Antagonists. Wright, *et al.* (127), described objective improvement in 24 of 91 patients, and 41 subjective improvements after treatment with aminopterin, amethopterin and amino-anfol for HD, leukemia and related neoplasms. Attention has already been directed to the combined therapy of folic acid antagonists and ACTH (40).

Diet. Gerson (44) studied the effect of diet on 8 patients with a variety of neoplasms, including HD.

Alpha-Peltatin. Greenspan, *et al.* (47, 48), obtained temporary regressions of HD with this agent.

Nitromin. Nasr and Awad (82) reported 2 of 3 patients treated with nitromin had complete remissions.

Triazine. Paterson and Boland (84) stated that trisethyleneimini-s-triazine was not superior to other agents in HD but they urged more clinical trials.

Butazolidin. Rottino, *et al.* (104), found phenylbutazone, or Butazolidin, was useful in controlling pain and fever, and in increasing the appetite and wellbeing of 35 HD cases.

Tissue Extracts. Rose (98) recorded marked clinical improvement in 5 HD patients injected with homogenate supernates from other HD patients.

Splenectomy. Sykes, *et al.* (117), stated that all 5 HD patients undergoing splenectomy had the course of the disease accelerated, and none responded later to HN_2 therapy or x-irradiation.

Guanazola. Straus, *et al.* (114), reported negative results with this agent on HD.

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SELECTED ABSTRACTS

An Evaluation of Steroid Preparations for Topical Therapy of Skin Eruptions. Robinson, H. M., Jr., Robinson, R. C. V., Strahan, J. F., and Cohen, M. M. *U. S. A. F. Med. J. 7*:963 (1956). Numerous steroid preparations have been developed during the past few years for use in the topical therapy of skin eruptions. The authors conducted a study on about 4000 patients to determine and compare the value of available steroid preparations.

The preparations were available in a variety of bases, including oily base ointments, greaseless base creams, and lotion bases. Formulas for these bases were given. Treatment was usually initiated with a steroid preparation of proven value, such as 1 per cent hydrocortisone or 0.1 per cent fludrocortisone (9 α-fluorohydrocortisone). After improvement was noted, either a placebo or one of the newer compounds was substituted without the patient's or physician's knowledge.

In an evaluation of bases, it was found that all of the bases employed were found to be satisfactory, except that two patients developed sensitivity reactions to a base containing hydrous wool fat. Hydrocortisone and its esters were used in the treatment of 1329 patients. Hydrocortisone free alcohol and hydrocortisone acetate were effective in the treatment of responsive dermatoses when applied locally in concentrations of 1 per cent or greater. Hydrocortisone hemisuccinate sodium and hydrocortisone diethylaminoacetate hydrochloride in concentrations of 0.5 per cent were approximately as effective as 1 per cent concentrations of the free alcohol or acetate.

Fludrocortisone acetate was found to be effective in the treatment of responsive dermatoses in 1067 patients when applied in concentrations of 0.1 per cent or greater. The difference between hydrocortisone and its esters and fludrocortisone appeared to be quantitative and not qualitative. 9-alpha fluorohydrocortisone tertiary butylacetate was also effectively used in 16 patients with a concentration of 0.5 per cent.

Initial studies with prednisolone and its succinate indicated that these compounds were relatively ineffective when applied topically to normally responsive dermatoses. In addition, a high incidence of primary irritation upon application was observed. However, when a more highly purified prednisolone was employed, a 0.5 per cent concentration was found to be as efficient as 1 per cent hydrocortisone. No primary irritation was observed with this purified compound.

A series of new complex chemical steroids called "allo compounds" were investigated. 9-alpha fluoro-allodihydrohydrocortisone acetate was found to be the most effective and the least irritating. However, the high incidence of primary irritation from this series of compounds probably will not make them useful for topical therapy.

The addition of antibiotics to preparations containing hydrocortisone, hydrocortisone acetate, fludrocortisone acetate and prednisolone were evaluated in 1753 patients. These combinations were effective in the treatment of responsive dermatoses complicated by secondary pyogenic infection. It was found that the antibiotic did not inhibit the action of the steroid and vice versa.

Combinations of hydrocortisone with Caligesic Lotion proved to be of little value because of primary irritation produced. Hydrocortisone in combination with Prantal Cream was valuable in the treatment of uncomplicated intertrigo. Combinations of fludrocortisone and hydrocortisone with coal tar were effective in the treatment of licheniform dermatitis.

Topical steroid therapy was found to be of definite value in the treatment of erythema solare, atopic dermatitis, dermatitis venenata, seborrheic dermatitis, intertrigo, pruritus ani, pruritus vulvae, lichen simplex chronicus, eczematous eruption of the hands, nummular eczema, stasis dermatitis, and eczematized epidermophytosis. It was of no value in psoriasis, lichen planus, chronic discoid lupus erythematosus, morphea, keratosis follicularis, pityriasis rosea, alopecia areata, epitheliomata, acne vulgaris, cutaneous fungus infections, pustular bacterid, herpes simplex, and verrucae.

The authors concluded that, in self-limited inflammatory conditions, the topical application of steroids provide immediate relief and may prevent the development of a chronic condition. In chronic dermatoses, topical application provides relief and control of the lesions but not permanent cure. Topical application may prevent the need for systemic therapy with steroids.

Timed-disintegration capsules, an in vivo Roentgenographic Study. Feinblatt, T. M. & Ferguson, E. A., Jr. *New England J. Med. 254:*940 (May 17, 1956). An in vivo roentgenographic study of time-disintegration capsules showed that, contrary to the common impression, the contents are scattered widely through the length of the gastro-intestinal tract before the individual particles disperse or dissolve. The popular belief that the mass of the capsule contents remains in a single blob, based on an artist's conception, is shown to be erroneous.

In the present study four different kinds of Nyscaps, (Nysco Timed-disintegration capsules), containing radiopaque barium sulfate 5 mg. (substituted for the usual active medication) were used. The first type was for immediate distintegration, the second for timed disintegration in about two hours, the third in about four hours, and the fourth in about six hours. Roentgenograms were taken immediately after ingestion and repeated in two, four, six, eight and ten hours.

The roentgenographic technique demonstrated a longer disintegration time than the modified U. S. P. method. The disintegration time was two to four hours as compared with two hours by U. S. P. technic, four to six hours as compared with four hours, and six to ten hours as compared with six hours. It is believed that the roentgenographic technic offers a more accurate picture because it is an in vivo method. The great convenience of the timed-disintegration capsule makes it an ideal method for the administration of drugs usually given in three divided doses.

The Treatment of Arteriosclerotic Syndromes Using Niacinamide Hydroiodide. Feinblatt, T. M., Feinblatt, H. M. & Ferguson, E. A. *Med. Times 84:*741 (July 1956). In a series of 50 cases of arteriosclerosis, the signs and symptoms which are partly reversible showed significant improvement after treatment for two months with parenteral niacinamide hydroiodide in combination with iodides. There was some alleviation of the condition in every case. The average age of the patients was 61, weight 157 lb. Significant relief of the following symptoms was observed: vertigo, depression, disorientation, excessive fatigue, vague abdominal distress, headache, emotional instability and anorexia. The medication used was Iodo-

Niacin ampuls 5 cc. twice weekly by intramuscular or slow intravenous injection. No untoward effects were observed and there was not a single case of iodism. Iodo-Niacin ampuls contain a combination of niacinamide hydroiodide with sodium iodide and niacinamide. The rationale of its use depends on the close relationship between iodism and pellagra, both of which are associated with porphyrinuria and impairment of the co-enzyme mechanism. The action of niacinamide hydroiodide in prevention of iodism is the same as that of niacinamide for pellagra. Reference is made to the report of an ophthalmologist who noted significant improvement of the retinal vessels following use of Iodo-Niacin.

Medication Administered By Means of Suppositories. Cacchillo, A. F. *U. S. A. F. Med. J. 7*:1009 (1956). The usefulness of suppositories for the administration of medicinal substances was discussed by the author. He indicated that suppositories were particularly well suited in infants and children, in persons unable to swallow capsules or tablets, in cases where the drugs interfere with digestive functions, and for drugs which are inactivated by digestive juices.

The author reported a comparison in blood levels of salicylate obtained in 11 subjects following the administration of acetylsalicylic acid in polyethylene glycol base suppositories, in cocoa butter base suppositories, in glycerinated gelatin base suppositories, and in oral tablets. In all cases the single dose was 0.64 Gm., one week apart. Using the blood level obtained from the administration of the oral tablets as 100 per cent, the average per cent absorption from the polyethylene glycol was 93.1, from cocoa butter was 65.5, and from glycerinated gelatin was 52.9. Thus, it would appear that absorption from the polyethylene glycol base suppository approached that from oral tablets.

The author spoke of the esthetic advantages of polyethylene glycol base suppositories and described their method of manufacture. He suggested that the base be composed of polyethylene glycols 6000, 1540, and 400 in the ratio 4-3-3. He provided formulas for polyethylene glycol base suppositories containing acetylsalicylic acid, chloral hydrate, aminophylline and pentobarbital sodium. For some reason

the "standard" suppository weight of 4 Gm. was used in developing all of the formulas.

The author concluded by listing the following advantages for polyethylene glycol base suppositories as compared with other bases: (1) greater degree of absorption, (2) no refrigeration required, (3) improved stability, and (4) greater pharmaceutical elegance and patient acceptability.

The Disposition of Dextran Following Intravenous Injection. Bloom, W. L. *J. Lab. and Clin. Med. 47*:938 (1956). The author reported on a series of studies performed to determine the disposition of dextran following intravenous injections. The carbohydrate partitions in the blood and urine were determined as well as the rate of disappearance of dextran from the blood and its appearance in the urine.

The partition of dextran between cells and plasma was studied first in rabbits and then in man. Carbohydrate levels, including total carbohydrate, dextran and reducing substances, were studied in the plasma of rabbits and in the plasma and urine of man. Dextran balance studies were also performed on a group of patients given 30 Gm. and on another group given 60 Gm.

The partition studies in both rabbits and man indicated that the dextran remained primarily extracellular in the blood stream, that is, in the plasma. An increase in the amount of reducing substances, indicating degradation products of dextran, was not found in blood or urine following the dextran injection. This did not prove that no such products were formed for the detection method may not have been sufficiently sensitive. However, if degradation products were formed they were present in very small quantities. During the first 24 hours following the injection, the urinary excretion of dextran was generally related to the urinary excretion of the polysaccharide. The excretion products were probably the fractions of lower molecular weight. Following this, the decrease in dextran concentration of the plasma was relatively fixed in magnitude being independent of the plasma levels resulting from the injection of 30 to 60 Gm. of dextran. About 50 to 150 mg. of dextran per 100 ml. of plasma were removed per day. Following the injection of 30 Gm. in 19 patients, an average

of 42 per cent of the dextran was excreted over a period of 5 days. Following the injection of 60 Gm. in 9 patients, an average of 48.6 per cent was excreted.

After the removal of the excretable fractions of dextran from the plasma, the remainder disappeared at a slow rate, indicating a rate limitation in metabolism, excretion, or removal by cells. This data indicated the persistence of dextran in the plasma for sufficient time to assure the efficacy of the material in plasma volume expansion.

Studies on the Respiratory Protection from Contagion Masks. Guyton, H. G., Buchanan, L. M., and Lense, F. T., *Applied Microbiol. 4*:141 (1956). Masks are commonly worn by surgeons, nurses, biological laboratory personnel, and pharmacists employing aseptic techniques. The wearing of these masks is intended to reduce the danger of the transmission of airborne pathogenic microorganisms. The effectiveness of three types of commercially available masks was studied by the authors. Type A consisted of a flexible aluminum frame to which was clamped a thin layer of absorbent cotton backed by a single thickness of gauze. Type B was a typical tie-on surgical mask with 4 thicknesses of gauze. Type C consisted of a single sheet of wax-impregnated paper held on the head by elastic loops placed around the ears.

The masks were tested in two ways, using spores of *Bacillus subtilis* var. *niger*. First, a nebulized aerosol of the spores was drawn into an aerosol chamber and through the mask by means of a vacuum for 5 minutes. A relative humidity of 50 per cent was maintained in the chamber. Any spores passing through the mask were collected on absorbent cotton in a glass tube. For control purposes spores were collected on another cotton wad in a glass tube. Also, the density of spores in the aerosol was determined. From these data, the per cent efficiency of the filter material was determined.

In the other test, human subject inhaled through their mouths and exhaled through their noses for 10 minutes. The masks were placed over their mouths during this period and a special cotton collector was placed in their mouths behind the masks. During the test period the patients performed sedentary work in a room with aerosolized spores of the test organism.

By the aerosol chamber test, the average percent efficiency of the masks was 48.4 for Type A, 42.7 for Type B, and 57.6 for Type C. The flow rate was 16 liters of air per minute through 13 sq. cm. of area. By the subject test, the average per cent efficiency was 38.0 for Type A, 17.6 for Type B, and 39.6 for Type C. The assumed breathing rate was 10 liters per minute. By contrast, using the human subject test, dust respirators and industrial masks gave from about 97 to 99.9 per cent efficiency.

A Study of the Comparative Effectiveness of Acetyl Sulfisoxazole Suspended in an Aqueous Medium and in an Oil in Water Emulsion. Svenson, S. E., Delorenzo, W. F., Engelberg, R., Spooner, M., and Randall, L. O. *Antibiot. Med. 2:*148 (1956). Comparative studies were undertaken on rats and on 12 adult human volunteers and 4 children as to the absorption and on mice for the chemotherapeutic effectiveness of acetylsulfisoxazole when suspended in an oil in water emulsion or in an aqueous medium. The oil in water emulsion contained 50 per cent vegetable oils with emulsifiers and the aqueous suspension contained acacia. The concentration of the drug was adjusted to 118 mg. of acetyl sulfisoxazole per ml., the equivalent of 100 mg. of sulfisoxazole. For comparison, sulfisoxazole itself was also given in both vehicles in some cases.

The absorption of acetylsulfisoxazole in both rats and human subjects was significantly greater, as indicated by blood level determinations, following the oral administration of the drug in the oil in water emulsion as compared with its administration in water at a period four hours after administration. Following this period the blood levels became practically the same. With sulfisoxazole there was little difference in the blood levels.

Chemotherapeutic experiments in mice against *Streptococcus pyogenes, Pneumococcus,* and *Salmonella schottmulleri* were performed using the acetyl derivative in both emulsion and aqueous vehicles. Against *Streptococcus pyogenes* the sulfonamide in the oil in water emulsion was over 5 times more effective than the aqueous suspension in protecting the mice. Over 900 mice were used in the tests. Against *Pneumococcus* the emulsion provided about 3 times the effectiveness. Against the *Salmonella schottmulleri* infection there was not significant difference in effectiveness.

A New Steroid Anesthetic. Lerman, L. H. *Brit. Med. J. No. 4985:*129 (1956). A new steroid anesthetic has been investigated clinically. It is 21-hydroxypregnane-3:20-dione sodium succinate (Viadril). This compound has been found to be a non-volatile crystalline solid, freely soluble in water, the solution having a pH of between 7.6 and 10.2. Pharmacologically, it has been found to have a wide margin of safety, the therapeutic index in mice being 11.1, as compared with 4.6 for thiopental sodium. It does not produce significant hormonal effects or salt retention in anesthetic doses. The known disadvantages of the compound are the slowness of induction of anesthesia and the risk of venous thrombophlebitis in the receiving vein.

The author reported the results obtained with this new anesthetic agent in 19 surgical cases of varying severity. In order to reduce the danger from thrombophlebitis the drug was injected into the tubing of the normal saline giving set. The dosage employed ranged from 500 to 1250 mg. of the drug. The induction of anesthesia resembled strikingly the coming of ordinary sleep. Further anesthesia was accomplished by a mixture of 3 parts nitrous oxide to 1 part oxygen. The relaxation obtained was good but not comparable to that obtained with the muscle relaxants. Bleeding was usually much reduced. After anesthesia was discontinued, the patient was usually awake and feeling well within an hour. A definite euphoria was obtained with this drug. Vomiting occurred in only one of the cases reported. Hormonal effects were absent.

BOOK REVIEWS

Methoden der Organischen Chemie (Houben-Weyl). Volume 3, Part I. Physikalische Forschungsmethoden. Fourth Edition. Edited by Eugen Müller. xxix + 954 pages, including 488 illustrations. Georg Thieme Verlag, Stuttgart, 1955. DM 162 (approximately $38).

This is the first of two books of the Houben-Weyl series which describe certain physical methods of investigation employed in organic chemistry; this book describes mechanical, thermal, microscopic, mass spectrometric, and isotopic methods. Sixteen chapters, each written by one or more specialists in the respective fields, deal with the following subjects: (1) Thermodynamic methods; (2) kinetic methods; (3) determination of density; (4) determination of solubility; (5) determination of vapor pressure; (6) determination of molecular weight of substances composed of small molecules; (7) determination of molecular weight of macromolecular substances; (8) surface tension and surface activity; (9) calorimetric methods; (10) determination of molecular configuration with the aid of molecular models; (11) consideration of errors of physical measurements; (12) microscopic and crystallochemical methods of investigation; (13) characterization and methods of study of liquid crystals; (14) mass-spectrophotometric methods; (15) estimation and use of radioactive atomic species in organic chemistry; (16) analytical determination and use of non-radioactive isotopes.

The theoretical basis of each subject is briefly but adequately reviewed, with the principal discussion being of methods (old and new) and of their utility in organic chemistry. The vast undertaking has been very capably performed and a meritorious book has been added to the literature of experimental chemistry. Probably every chemist working in a laboratory will have occasion to utilize techniques described in this volume and will in all likelihood find helpful information concerning them.

ARTHUR OSOL

Methoden der Organischen Chemie (Houben-Weyl). Volume 9. Schwefel-, Selen-, Tellur-Verbindungen. Fourth Edition. Edited by Eugen Müller. xxxi + 1337 pages, including 9 illustrations. Georg Thieme Verlag, Stuttgart, 1955. DM 218 (approximately $52).

A total of 915 pages of this volume of the Houben-Weyl series deals with the preparation and reactions of all classes of organic sulfur compounds; a section of 292 pages provides the same type of information about organic selenium and tellurium compounds. Preparative methods specify quantities of reactants to be employed, as well as conditions of interaction; literature and patent references indicate the origin of the methods. For the most part the pertinent journal and patent literature has been reviewed to 1954, although much of it, including that pertaining to organic selenium and tellurium compounds, has been reviewed to 1955. This volume maintains the high standard of excellence of the distinguished series of books on organic chemistry of which it is a unit.

ARTHUR OSOL

Blakiston's New Gould Medical Dictionary, Second Edition. Editors Normand L. Hoerr and Arthur Osol. 1463 pages, including tables. McGraw-Hill Book Company, Inc., New York, Toronto, and London, 1956. $11.50.

The first edition of the *New Gould Medical Dictionary* by Blakiston appeared in 1949. It was a completely new and modern version of the old and well-known series of medical dictionaries begun by Gould in 1890. From the day of its release, Blakiston's New Gould became the standard work of its kind in the United States and it has enjoyed a well-deserved popularity.

The second edition, coming seven years later, has maintained the high quality of workmanship seen in the 1949 edition. The editorial board was assisted by 88 contributors, each himself a recognized authority in his field. Over 12,000 new terms have been added together with 8,000 changes in usage, spelling, etc. While this is a great achievement, it was of course necessary in view of the changes in medical science in the last eight or nine years.

Some of the fields represented in the wealth of new terms are psychiatry, nuclear science, anti-arthritic drugs, and cancer therapy. The use of U. S. P. XV and N. F. X terms throughout is useful and proprietary names are given wide coverage.

No worker in any of the many fields of medical science can read or write without frequent reference to an authoritative medical dictionary. To the student, such a book is even more essential. Blakiston's New Gould is without doubt the top ranking medical dictionary in the United States.

L. F. Tice

Basic Principles of Parliamentary Law and Protocol by Marguerite Grumme, Registered Parliamentarian. 68 pages, including index. Marguerite Grumme, St. Louis 16, Missouri, 1955. $1.00.

In America today, there are literally hundreds of thousands of organizations, each having its own officers and expected to conduct its affairs in an efficient, businesslike, and correct manner. Few people, unless they have had wide experience, are familiar with the duties of officers, proper protocol, and parliamentary procedure.

This little booklet by Miss Grumme would prove of great value to anyone faced for the first time with the duties of office in an organization and, most particularly, with the responsibility of presiding over a meeting. While there are some rather large treatises on parliamentary law, they are written in such a heavy style as to make it very difficult for the average layman to understand them. This booklet is very simple and written in straightforward, clear language that anyone can understand. The author, who is a registered parliamentarian and who has served as an officer in a number of organizations, has also lectured on parliamentary law and protocol, and it is evident to the reader that her written text is based upon a wealth of experience and on an exhaustive knowledge of the subject.

To those who are concerned and somewhat confused over the responsibilities of holding an office and carrying out their assignment properly, we wholeheartedly recommend this book. It seems even better for the beginner than some of the more widely known and authoritative works on the subject.

L. F. Tice

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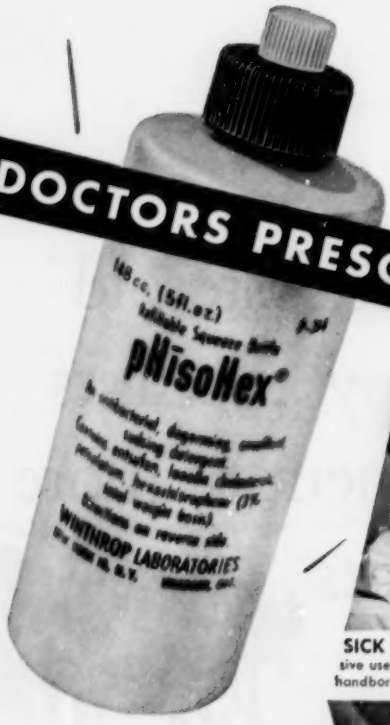

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